SYSTEM, METHOD AND APPARATUS FOR SMALL PULMONARY NODULE COMPUTER AIDED DIAGNOSIS FROM COMPUTED TOMOGRAPHY SCANS

This application claims the benefit of U.S. Provisional Application No.60/419,597, filed October 18, 2002, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to the art of diagnostic imaging of small pulmonary nodules. In particular, the present invention is related to analyzing and manipulating computed tomography scans to: detect lung nodules and correlate a pair of segmented images of a lung nodule obtained at different times.

Lung cancer is the leading cause of cancer death in the United States. According to the American Cancer Society, there were approximately 169,400 new cases of lung cancer (90,200 among men and 79,200 among women) in the United States in the year 2002. About 154,900 lung cancer deaths were predicted for the same year, which accounts for 28% of all cancer deaths. Although survival rate of lung cancer is only 14%, results from the ELCAP project show that detection and treatment of lung cancer at early stages may improve this rate to 70%. C. I. Henschke, D. I: McCauley, D. F. Yankelevitz, D. P. Naidich, G. McGuinness, O. S. Miettinen, D. M. Libby, M. W. Pasmantier, J. Koizumi, N. K. Altorki, and J. P. Smith. "Early Lung Cancer Action Project: overall design and findings from baseline screening." Lancet July 10, 1999; 354(9173):99-105. Hence, lung cancer screening has recently received considerable attention.

In the screening process, radiologist analyze images of asymptomatic patients searching for a specific abnormality. Henschke et al reported that using low-dose CT as compared to chest radiography can improve the detection of small,

non-calcified nodules at potentially more curable stage. Claudia. I. Henschke, D. P. Naidich, D. F. Yankelevitz, G. McGuinness, D. I. McCauley, J. P. Smith, D. M. Libby, M. W. Pasmantier, M. Vazquez, J. Koizumi, D. Flleder, N. K. Altorki, and O. S. Miettinen, "Early Lung Cancer Action Project: Initial Findings on Repeat Screening." Cancer July 1, 2001; 92(1):153-159. The introduction of Computed Tomography (CT) scanners, particularly scanners with helical capabilities, has increased the resolution of lung images and greatly increased the number of images per screening study that must be evaluated by the radiologist. The development of the computed tomography (CT) technology and post-processing algorithms has provided radiologists with a useful tool for diagnosing lung cancers at early stages. However, current CT systems have their inherent shortcomings in that the amount of chest CT images (data) that is generated from a single CT examination, which can range from 30 to over 300 slices depending on image resolution along the scan axial direction, becomes a huge hurdle for the radiologists to interpret. Accordingly, there is a constant need for the improvement and development of diagnostic tools for enabling a radiologist to review and interpret the vast amount of information that is obtained through a CT examination.

International Publication No. WO 01/78005 A2 discloses a system and method for three dimensional image rendering and analysis, and is incorporated herein by reference. The system performs a variety of tasks that aid a radiologist in interpreting the results of a CT examination.

U.S. Patent Application Serial No.10/245,782 discloses a system and method directed to diagnostic imaging of small pulmonary nodules, and is incorporated herein by reference. The application includes methods for detection and feature extraction for size characterization, and focuses on the analysis of small pulmonary nodules that are less than 1 centimeter in size, but is also suitable for larger nodules as well.

Radiologist generally fail to detect nodules primarily due to interpretation and oversight error. The use of a computer aided detection (CAD) systems avoids these human related errors to tremendously improve diagnostic accuracy. M. Fiebich,

C. Wietholt, B.C. Renger, S.G Armato, K.R. Hoffmann, D. Wormanns and S. Diederich, "Automatic detection of pulmonary nodules in low-dose screening thoracic CT ex-aminations", *SPIE*, vol. 3661, pp 1434-1439, 1999; S.G Armato, 111, F. Li, M.L. Giger, "Performance of Automated CT Lung Nodule Detection on Missed Cancers", scientific paper presentation, RSNA 87th scientific assembly and annual meeting, Nov 25 -30, 2001; F. Li, S. Sone, H. Abe, H.M MacMahon, S.G Armato, K. Doi, "Missed Lung Cancers in low-dose Helical CT Screening Obtained from a General Population", scientific paper presentation, RSNA 87th scientific assembly and annual meeting, Nov 25 -30, 2001; C.L Novak, D.P Naidich, L. Fan, J. Qian, J.P. Ko, A.N Rubinowitz, "Improving Radiologists' Confidence of Interpreting Low-dose Multidetector Lung CT screening Studies Using an Interactive CAD system", Scientific paper presentation, RSNA 87th scientific assembly and annual meeting, Nov 25 -30, 2001. CAD systems perform automated nodule detection in addition to providing useful visualization tools for the radiologists.

Novak et al reported an improvement in detection of potential nodules from 22 to 77% with the availability of an interactive CAD (ICAD) system for the radiologist. C.L Novak, D.P Naidich, L. Fan, J. Qian, J.P. Ko, A.N Rubinowitz, "Improving Radiologists' Confidence of Interpreting Low-dose Multidetector Lung CT screening Studies Using an Interactive CAD system", Scientific paper presentation, RSNA 87th scientific assembly and annual meeting, Nov 25 -30, 2001. Potential nodules were identified and rated with and without the ICAD tools for nodule interpretation. They concluded from their results that the interactive CAD systems significantly increase radiologists confidence when interpreting CT screening studies. In another study, Aramato et al reported that 78% of nodules missed during visual interpretation were detected by their automated method. 72% of the missed nodules were due to oversight' error, and the rest were due to interpretation error. S.G Armato,111, F. Li, M.L. Giger, "Performance of Automated CT Lung Nodule Detection on Missed Cancers", scientific paper presentation, RSNA 87th scientific assembly and annual meeting, Nov 25 -30, 2001. All the nodules missed due to oversight error were detected by their CAD system whereas 70% of the nodules missed due to interpretation error were detected. Li et al also showed that 78% of missed nodules

were detected by their computerized scheme. F. Li, S. Sone, H. Abe, H.M MacMahon, S.G Armato, K. Doi, "Missed Lung Cancers in low-dose Helical CT Screening Obtained from a General Population", scientific paper presentation, RSNA 87th scientific assembly and annual meeting, Nov 25 -30, 2001. According to them, the main reason for detection errors were difficulty in detection due to small size and low intensity, oversight due to adjacent or overlapping pulmonary vessels or fissures and lack of attention to relatively obvious nodules adjacent to the pulmonary hilum. In a related study, Fiebich et al reported a 15% improvement in detection sensitivity using their CAD system in addition the conventional film reading procedure. M. Fiebich, C. Wietholt, B.C. Renger, S.G Armato, K.R. Hoffmann, D. Wormanns and S. Diederich, "Automatic detection of pulmonary nodules in low-dose screening thoracic CT ex-aminations", *SPIE*, vol. 3661, pp 1434-1439, 1999.

The evolution of CT scanner technology has played an important role in the development of detection algorithms. Early low resolution whole lung CT scans had a slice thickness of 5-10mm with a 0.5-0.6 mm in-plane resolution. Because of this low axial resolution, early computer detection algorithms were based entirely on two dimensional (slice-by-slice) image analysis techniques. Currently, multi-slice helical scanners with better axial resolution are widely available. This improvement in axial resolution permits three dimensional image analysis techniques which can detect smaller nodules.

Recent research on pulmonary nodule detection has focused on 3D region identification and feature extraction procedures followed by rule-based classification. Aramato et al implemented a computerized scheme that uses 2D and 3D extracted features from regions identified by multiple level gray-level thresholding. S.G. Armato III, M. L. Giger, J.T Blackburn, K. Doi, H. MacMahon, "Three-dimensional approach to lung nodule detection in helical CT", *SPIE*, vol. 3661, pp. 553-559, 1999. In this paper, they used a rolling ball algorithm to avoid missing nodules attached to the pleural surface. They reported an operating point of 85% sensitivity and 89% specificity indicating an overall sensitivity of 70% with an average of three false-positive per slice. Similarly, 2D and 3D geometrical features have been used by

Gurcan et al in their detection algorithm. M.K. Gurcan, N. Petrick, B. Sahiner, H.P. Chan, P.N. Cascade, E.A. Kazerooni, L.M. Hadjiiski, "Computerized lung nodule detection on thoracic CT images: combined rule-based and statistical classifier for false positive reduction", *SPIE*, Vol. 4322, pp 686-692, 2001. They reported a 84% detection rate with 1.75 FPs per slice detection results tested on 17 patients with a total of 31 lung nodules. Fan et al implemented an adaptive 3D region growing algorithm followed by a classification scheme that makes use of geometric features such as diameter, volume, sphericity, mean intensity value and standard deviation of intensity. L. Fan, C. Novak, J. Qian, G. Kohl and D. Naidich, "Automatic Detection of Lung Nodules from Multi-Slice Low-Dose CT Images", *SPIE*, vol.4322, pp 1828-1835, 2001. This algorithm only detects nodules with very small vasculature connections and no large solid structure attachment. Toshioka et al tested their detection algorithm which on 450 cases (15,750 images). S. Toshioka, K. Kanazawa, N. Niki, H. Satoh, H. Ohmatsu, K. Eguchi, et al, "Computer aided diagnosis system for lung cancer based on helical CT images", *SPIE*, vol. 3034, pp 975-984, 1997. Compared with image interpretation by 3 Radiologists, CAD detected all tumors identified as highly probable with 5 false negatives (4 of which represented tumors less than 5mm in size) and 11 false positive cases(ranging from 2.4/case for "high probability" nodules to 7.2/case for "suspicious" nodules).

Lee et al used a template matching technique based on a genetic algorithm to detect nodules. Different templates were generated for nodules with and without an attachment to the pleural surface. Y. Lee, T. Hara, H. Fujita, S. Itoh and T. Ishigaki, "Automated Detection of Pulmonary Nodules in Helical CT images Based on an Improved Template-Matching Technique", IEEE Transactions on Medical Imaging, Vol. 20, No. 7, pp 595-604, 2001. Although, they developed an elegant mathematical model of a nodule, the algorithm resulted in a very high number of false positives (4.4 per slice) with 72% sensitivity. Other computer vison methods have also been explored for pulmonary nodule detection. Morphological analysis techniques have been utilized for detection of suspicious regions. H. Taguchi, Y. Kawata and N. Niki, H. Satoh, H. Ohmatsu, K. Eguchi, M. Kaneko and N. Moriyama, "Lung cancer detection based on helical CT images using curved surface morphology analysis",

SPIE, vol 3661, pp 1307-1313, 1999. Penedo et al have developed a computer aided detection system based on a two level artificial neural network. M.G. Penedo, M.J. Carreira, A. Mosquera, and D. Cabello, "Computer-aided diagnosis: a neuralnetwork based approach to lung nodule detection", IEEE Transactions on Medical Imaging, vol.17, no.6, pp 872-879, 1998. The first network performs detection of suspicious regions, while the second one classify the regions based on the curvature peak on all points in the suspicious region. They recorded 89% - 96% sensitivity with 5-7 FPs per slice. Artificial neural networks' capabilities have also been used by Lo et el. S-C B. Lo, S-L A. Lou, J-S Lin, M.T. Freedman, M V. Chien and S. K. Mun, "Artifical convolution neural Network techniques and applications for lung nodule detection", - IEEE transactions on medical imaging, vol. 14, no.4, pp 711-718, 1995. In their work, Lo et al used a convolution type neural network which recorded an 82% detection rate.

Object-based deformation techniques have been incorporated into detection systems. Lou et al used deformation techniques to differentiate lung nodules from blood vessels in their 3D CT lung nodule detection system. S.L Lou, C.L Chang, K.P Lin and T. Chen, "Object based deformation technique for 3-D CT lung nodule detection", *SPIE*, vol 3661, pp 1544-1552.1999. This research did not address surface irregularities that occur in nodules with significant vasculature connections. Knowledge based techniques have also been used in recent research. Works of Erberich et al and Brown et al can be cited in this regard. S.G. Erberich, K.S. Song, H. Arakawa, H.K Huang, R. Webb, K. S. Hoo, B.W. Loo, "knowledgebased lung nodule detection from helical CT", RSNA 1997 annual meeting; M.S. Brown and M. F. McNitt-Gray, "Method for segmenting chest CT image data using an anatomical model: preliminary results", *SPIE*, vol-16, no.6, pp 828-839, 1997. Erberich et al used rule based tree to classify candidates generated using gradient Hough transformation. Detection performance statistical results were not reported in their paper. Brown et al developed a multipurpose modular knowledge based system. They demonstrated nodule detection application using this modular architecture.

A review of the prior art indicates that progress has been made on developing automated detection programs for lung nodules in helical CT scans. However, there is a large variations in performance, likely caused by the small data sets used in these studies. Much more effort is need to bring the performance of these computerized detection systems to level acceptable for clinical implementation. Most of the detection algorithms have been designed to detect a single type of a nodule (i.e nodule with a small vessel connection). Nodules with significant vessel connections or attachment to large solid structure have been either reported as a missed or not considered in the detection performance evaluation. Y. Lee, T. Hara, H. Fujita, S. Itoh and T. Ishigaki, "Automated Detection of Pulmonary Nodules in Helical CT images Based on an Improved Template-Matching Technique", IEEE Transactions on Medical Imaging, Vol.20, No.7, pp 595-604, 2001; L. Fan, C. Novak, J. Qian, G. Kohl and D. Naidich, "Automatic Detection of Lung Nodules from Multi-Slice Low-Dose CT Images", *SPIE*, vol.4322, pp 1828-1835, 2001; M. Fiebich, C. Wietholt, B.C. Renger, S.G Armato, K.R. Hoffmann, D. Wormanns and S. Diederich, "Automatic detection of pulmonary nodules in low-dose screening thoracic CT examinations", *SPIE*, vol. 3661, pp 1434-1439, 1999. Accordingly, there is a great need for an algorithm which detects nodules with or without attachments to large solid structures with fewer false positives.

One predictor of malignancy of a pulmonary nodule in a CT image is the change in volume of the nodule. The change in volume can be measured as percent volume change or a doubling time. To obtain these measurements, two high-resolution CT scans, separated by a few months, are taken of the nodule. The nodules are segmented from the CT images and the percent volume change or doubling time is calculated using the segmented nodule volumes. The accuracy of the change in volume measurement is dependent on the consistency of the segmentations of the nodule in the two images. In the extreme case, a missegmentation of one of the nodules may adversely affect the malignancy predictor by moving the doubling time measurement above or below the threshold for malignancy.

There has been some work on tracking the change of pulmonary nodules in CT images. In Kawata et al, the pulmonary nodules are registered together using rigid-body registration and affine registration at two different stages. Y. Kawata, N. Niki, H. Ohmatsu, M. Kusumoto, R. Kakinuma, K. Mori, N. Nishiyama, K. Eguchi, M. Kaneko, and N. Moriyama. Tracking interval changes of pulmonary nodules using a sequence of three-dimensional thoracic images. In *Medical Imaging 2000: Image Processing, Proceedings of SPIE,* volume 3979, pages 86-96, 2000. The nodules are segmented using a 3-D deformable surface model and curvature features are calculated to track the temporal evolution of the nodule. This work was extended by Kawata et al, by adding an additional 3-D non-rigid deformable registration stage and the analysis was performed using a displacement field to quantify the areas of nodule growth over time. Y. Kawata, N. Niki, H. Ohmatsu, M. Kusumoto, R. Kakinuma, K. Mori, N. Nishiyama, K. Eguchi, M. Kaneko, and N. Moriyama. Analysis of evolving processes in pulmonary nodules using a sequence of three-dimensional thoracic images. In M. Sonka and K. M. Hanson, editors, *Medical Imaging 2001: Image Processing, Proceedings of SPIE,* volume 4322, pages 1890-1901, 2001. In Reeves et al, a method was introduced to estimate the growth of a nodule without the explicit use of segmentation. A. P. Reeves, W. J. Kostis, D. F. Yankelevitz, and C. I. Henschke. Analysis of small pulmonary nodules without explicit segmentation of CT images. *Radiology,* 217P:243-244, November 2000. The pulmonary nodules are registered using translation and the doubling time is calculated from the gaussian-weighted regions-of-interest. In Kostis et al, and Reeves et al, a segmentation method based on thresholding and morphological filtering is discussed. W. J. Kostis, A. P. Reeves, D. F. Yankelevitz, and C. I. Henschke. Three-dimensional segmentation of solitary pulmonary nodules from helical CT scans. In H. U. Lemke, M. W. Vannier, K. Inamura, and A. G. Farman, editors, *Proceedings of Computer Assisted Radiology and Surgery (CARS '99),* pages 203-207. Elsevier Science, June 1999; A. P. Reeves and W. J. Kostis. Computer-aided diagnosis of small pulmonary nodules. *Seminars in Ultrasound, CT, and MRI,* 21(2):116-128, April 2000. From the nodule segmentation, the volume of the nodule can be easily calculated and the doubling-time can be determined.

SUMMARY OF THE INVENTION

The present invention is directed to diagnostic imaging of small pulmonary nodules. There are two main stages in the evaluation of pulmonary nodules from CT scans: detection, in which the locations of possible nodules are identified, and characterization, in which a nodule is represented by measured features that may be used to evaluate the probability that the nodule is cancer. Currently, the most useful prediction feature is growth rate, which requires the comparison of size estimates from two CT scans recorded at different times. The present invention includes methods for detection and feature extraction for size characterization. The invention focuses on small pulmonary nodules that are less than 1 centimeter in size, but these methods are also suitable for larger nodules as well.

For the purpose of Computer Aided Diagnosis (CAD), Pulmonary nodules are dichotomized into attached nodules and isolated nodules based on their location with respect to other solid lung structures. Attached nodules are adjacent to some larger solid structure, such as the pleural surface. Isolated nodules consist of both well-circumscribed nodules and nodules that are larger than all adjacent structures, such as blood vessels or bronchi. The nodules may be solid, non-solid or part-solid. The overall analysis of a Computed Tomography scan generally entails the following:

1. Detection

(a) Identify the lung regions and main bronchi from thoracic CT images

(b) Separate the lungs into two major regions: (1) the lung parenchyma and (2) the lung surface region, including the pleural surface and major airways.

(c) Identify possible locations of isolated nodules in the lung parenchyma region and identify possible locations of attached nodules in the in the lung surface regions.

2. Characterization

(a) Starting with a single location point within a possible nodule, identify the nodule region in the CT images. This entails locating the geometric center of the nodule and approximating its size.

(b) Given the location and approximate size of a nodule, compute characteristic features of the nodule, including robust size estimates.

The present invention identifies possible locations of isolated nodules in the lung parenchyma region within whole lung CT scans. With reference to the overall analysis listed above, this aspect corresponds to the first part of task 1(c). In particular, the invention addresses the detection problem of isolated nodules and expands upon the lung segmentation algorithms disclosed in United States Patent application serial no. 10/245,782. The invention searches the segmented lung region with a filter to identify lung nodule candidates. A set of filters then eliminate a substantial amount of false candidates until only those with a high probability of being true nodules remain.

The present invention also includes methods for improving the consistency of pulmonary nodule segmentation using 3D rigid-body registration. The accurate repeat segmentation of lung nodules is critical to the measurement of nodule growth rate, which is the most accurate non-invasive computer based predictor of malignancy. The invention increases the accuracy of repeat segmentation by image comparison methods including (a) 3D rigid body registration, (b) histogram matching, and (c) knowledge-based matching of the vessel removal.

A preferred embodiment of the present invention is a method and apparatus for analyzing a computed tomography scan of a whole lung for lung nodules. The apparatus of the invention is a detecting unit configured with the teachings of the method of the invention. The invention can also be practiced on a machine readable medium. The method includes segmenting a first lung region and a second lung region from the computed tomography scan. The first lung region corresponds to lung parenchyma of the lung and the second lung region corresponds to at least one of

a pleural surface of the lung and a surface defined by vessels within the lung. An initial list of nodule candidates is generated from the computed tomography scan within the first lung region. The list includes at least a center location and an estimated size associated with each nodule candidate. Subimages are next generated for each nodule candidate in the initial list. Streaking artifacts are then selectively removed from the subimages. The nodule candidates are filtered to eliminate false positives from the list.

In a preferred embodiment, the initial list is generated by thresholding the first lung region. Nodule candidate regions are next identified by labeling high density voxels foreground voxels. $\hat{R}_{MI}$ is determined for each foreground voxel. The local maximum $\hat{R}_{MI}$ is selected within a nodule candidate region. The limited extent criterion is next determined for each foreground voxel which corresponds to a $\hat{R}_{MI}$. The initial list of nodule candidates is generated for nodules which satisfy the limited extent criterion. The list includes at least Nc and $\hat{R}_{MI}$ associated with the corresponding foreground voxel.

In another preferred embodiment, the streaking artifact removal is accomplished by initially determining the amount of streaking artifact present in the sub-image followed by filtering the streaking artifact out from the subimage when the amount of the streaking artifact present in the sub-image exceeds Tsar. Preferably the amount of streaking artifact present in the sub-image is calculated by a metric

$$S_m = \frac{1}{nmp}\sum_{i}^{n}\sum_{j}^{m}\sum_{k}^{p}\left((I(i,j,k) - I(i,j+1,k)\right)^2$$

Preferably the filtering is performed by a vertical median filter of size 1x3 and T_{sar} is selected to be in a range from about 20000 to about 80000.

In another preferred embodiment, the false positives are eliminated from the list by initially determining for each nodule candidate a fraction, F_a, of a surface of

the nodule candidate that is attached to other solid structures followed by removing the nodule candidate from the list when the fraction exceeds T_a.

In another preferred embodiment, the false positives are eliminated from the list by initially generating a cube wall about each nodule candidate followed by determining an intersection volume, V_{ni}, corresponding to portions of the nodule region associated with the nodule candidate that intersect the cube wall. Nodule candidates are removed from the list when the fraction of the intersection volume, V_{ni}, over the volume of the nodule candidate, V_n, exceeds T_{vv}.

A preferred embodiment of the present invention is a method and apparatus for correlating a segmentation of 3-d images of a pulmonary nodule from a high-resolution computed tomography (CT) scans. The images include a first image (im_1) obtained at time-1 and a second image (im_2) obtained at time-2. The apparatus of the invention is a registration unit configured with the teachings of the method of the invention. The invention can also be practiced on a machine readable medium. The method includes selecting a first region-of-interest (ROI_1) for the nodule in the first image (im_1) and selecting a second region-of-interest (ROI_2) for the nodule in the second image (im_2). The second region-of-interest (ROI_2) is registered to the first region-of-interest (ROI_1) to obtain a transformed second region-of-interest (ROI_{2t}). The nodule in the first region-of-interest (ROI_1) and the transformed second region-of-interest (ROI_{2t}) are both separately segmented. The first segmented nodule (S_1) and the second segmented nodule (S_2) are then adjusted.

In a preferred embodiment, the nodule in the first region-of-interest (ROI_1) and the transformed second region-of-interest (ROI_{2t}) are both separately segmented by performing at least one of the following:

(i) gray-level thresholding;

(ii) morphological filtering for vessel removal: and

(iii) plane clipping for separarting a pleural wall.

Preferably the gray-level thresholding is performed at an adaptive threshold level. The adaptive threshold level is preferably selected for each region-of-interest (ROI_1 and ROI_2) by:

determining a peak parenchyma value, v_p;

determining a peak nodule value, v_n;

calculating the adaptive threshold level as a midpoint between the peak parenchyma value, v_p, and the peak nodule value, v_n.

An intensity histogram, $H(x)$ is preferably calculated for determining the peak parenchyma value, v_p, and the peak nodule value, v_n. The intensity histogram, $H(x)$, is preferably filtered with a gaussian with standard deviation of about 25 HU prior to determining the peak parenchyma value, v_p, and the peak nodule value, v_n.

In another preferred embodiment, the registration to obtain a transformed second region-of-interest (ROI_{2t}) is performed by:

(a) calculating initial rigid-body transformation parameters for a rigid-body transformation on the second region-of-interest (ROI_2);

(b) determining the optimum rigid-body transformation parameters by calculating a registration metric between the first region-of-interest (ROI_1) and the rigid-body transformation on the second region-of-interest (ROI_2); and

(c) generating a registered image from the optimum rigid-body transformation parameters.

Preferably the registration metric is calculated by:

transforming the second region-of-interest (ROI_2) with the initial rigid-body transformation parameters to obtain a transformed second region-of-interest (ROI_{2t});

calculating the registration metric as a mean-squared-difference (MSD) between the transformed second region-of-interest (ROI_{2t}) and the first region-of-interest (ROI_1); and

searching for the minimum mean-squared-difference (MSD) in the 6-dimensional parameter space.

The transforming of the second region-of-interest (ROI_2) to obtain the transformed second region-of-interest (ROI_{2t}) is preferably a mapping of a point v in 3-d space to a point v' in transformed space defined by :

$$v'=RxRyRzv+\begin{bmatrix} tx \\ ty \\ tz \end{bmatrix}$$

wherein Rx, Ry, and Rz are rotation matrices defined as:

$$R_x = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(r_x) & -\sin(r_x) \\ 0 & \sin(r_x) & \cos(r_x) \end{bmatrix}$$

$$R_y = \begin{bmatrix} \cos(r_y) & 0 & \sin(r_y) \\ 0 & 1 & 0 \\ -\sin(r_y) & 0 & \cos(r_y) \end{bmatrix}$$

$$R_z = \begin{bmatrix} \cos(r_z) & -\sin(r_z) & 0 \\ \sin(r_z) & \cos(r_z) & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

The initial rigid-body transformation parameters preferably include six parameters (tx,ty,tz,rx,ry,rz) respectively defined as translation in x, translation in y, translation in z, rotation about the x-axis, rotation about the y-axis, and rotation about the z-axis. The initial rotation parameters (rx,ry,rz) are generally all set to zero while the initial translation parameters $(tx,ty,tz,)$ are set so that the nodule in the first region-of-interest (ROI_1) overlaps the nodule in the second region-of-interest (ROI_2) during the initial calculation of the registration metric. Preferably the mean-squared-difference (MSD) is gaussian weighted.

In another preferred embodiment, a first thresholded image (T_1)and a second thresholded image (T_2) are defined by gray-level thresholding prior to vessel removal and separating the pleural wall. The adjustment of first segmented nodule (S_1) and the second segmented nodule (S_2) is performed by comparing the segmented nodules and the thresholded images. The active pixels in the segmented nodules are marked as one of:

a repeat nodule pixel;

a nodule growth pixel;
a nodule atrophy pixel; and
a nodule missegmentation pixel.

A foreground pixel in the first segmented nodule (S_1) is preferably marked as a repeated nodule pixel from the first region-of-interest (ROI_1) to the transformed second region-of-interest (ROI_{2t}) when the corresponding pixel in second segmented nodule (S_2) and the corresponding pixel in second thresholded image (T_2) are both foreground. A foreground pixel in the first segmented nodule (S_1) is preferably marked as a nodule atrophy pixel when the corresponding pixel in second segmented nodule (S_2) is background and the corresponding pixel in second thresholded image (T_2) is background. A foreground pixel in the first segmented nodule (S_1) is preferably marked as a missegmented pixel in the first region-of-interest (ROI_1) when the corresponding pixel in second segmented nodule (S_2) is background and the corresponding pixel in second thresholded image (T_2) is foreground. A foreground pixel in the second segmented nodule (S_2) is preferably marked as a repeated nodule pixel from the first region-of-interest (ROI_1) to the transformed second region-of-interest (ROI_{2t}) when the corresponding pixel in first segmented nodule (S_1) and the corresponding pixel in first thresholded image (T_1) are both foreground. A foreground pixel in the second segmented nodule (S_2) is preferably marked as a nodule growth pixel when the corresponding pixel in first segmented nodule (S_1) is background and the corresponding pixel in first thresholded image (T_1) is background. A foreground pixel in the second segmented nodule (S_2) is preferably marked as a missegmented pixel in the transformed second region-of-interest (ROI_{2t}) when the corresponding pixel in first segmented nodule (S_1) is background and the corresponding pixel in first thresholded image (T_1) is foreground.

For a better understanding of the present invention, reference is made to the following description to be taken in conjunction with the accompanying drawings and its scope will be pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the invention have been chosen for purposes of illustration and description and are shown in the accompanying drawings, wherein:

Figure 1 is a flowchart of the automated detection algorithm;

Figure 2 is an original single axial image scan;

Figure 3 illustrates the lung parenchyma after being segmented from the image shown in Figure 2;

Figure 4 illustrates the pleural surface corresponding to the surface of the volume shown in Figure 3;

Figure 5 illustrates an isolated pulmonary nodule;

Figure 6 illustrates an pulmonary nodule attached to pleural surface;

Figure 7 is a 2-dimensional illustration of R_{MI} *and* R_{MC};

Figure 8 is a 2-dimensional illustration of volume occupancy procedure;

Figure 9 illustrates the spherical shell used for nodule adjacent region analysis;

Figure 10 illustrates a nodule sub-image before streaking artifact removal;

Figure 11 illustrates a nodule sub-image after streaking artifact removal;

Figure 12 illustrates a multi-stage filtering procedure for successive refinement of the nodule candidates;

Figure 13 illustrates nodule candidate attachment analysis;

Figure 14 illustrates the region growing procedure for the attachment analysis;

Figure 15 illustrates the effect of global thresholding on small vessel bifurcation points on the original gray scale image;

Figure 16 illustrates the effect of global thresholding on small vessel bifurcation points on the binary image;

Figure 17 illustrates small bifurcation point removal;

Figure 18 is a histogram of a real 12mm nodule between -1200HU and 200 HU;

Figure 19 is a histogram of a real 12mm nodule between -200HU and 200HU;

Figure 20 is a histogram of an ideal nodule between -1200HU and 200 HU;

Figure 21 is a histogram of an ideal nodule between -1200HU and 200 HU;

Figure 22 is a histogram of a real 5mm nodule between -1200HU and 200HU;

Figure 23 is a histogram of a real 5mm nodule between -200HU and 200HU;

Figure 24 illustrates an image of the rigid-body registration of the first ROI;

Figure 25 illustrates an image of the rigid-body registration of the second ROI;

Figure 26 illustrates an image of the rigid-body registration of the second ROI registered to the first ROI;

Figure 27 illustrates the difference image between the first ROI and the second ROI;

Figure 28 illustrates the difference image between the first ROI and the registered second ROI;

Figure 29 illustrates a montage of the original gray scale image showing the nodule region-of-interest;

Figure 30 illustrates a montage showing the segmented nodule corresponding to Figure 31;

Figure 31 illustrates a first thresholded image (T_1) corresponding to the first region-of-interest (ROI_1);

Figure 32 illustrates a second thresholded image (T_2) corresponding to the transformed second region-of-interest (ROI_{2t});

Figure 33 illustrates a first segmented nodule (S_1) corresponding to the first region-of-interest (ROI_1);

Figure 34 illustrates a second segmented nodule (S_2) corresponding to the transformed second region-of-interest (ROI_{2t});

Figure 35 illustrates the first segmented nodule (S_1) having the active pixels therein marked as (A) nodule in time 1, (B) nodule atrophy, or (C) missegmentation;

Figure 36 illustrates a second segmented nodule (S_2) having the active pixels therein marked as (D) nodule in time 2, (E) nodule growth, or (F) missegmentation;

Figure 37 illustrates a first adjusted segmented nodule (N_1) corresponding to the first region-of-interest (ROI_1); and

Figure 38 illustrates a second adjusted segmented nodule (N_2) corresponding to the transformed second region-of-interest (ROI_{2t}).

DETAILED DESCRIPTION OF THE INVENTION

A system in accordance with the present invention may include a scanner, processor, memory, display device, input devices, such as a mouse and keyboard, and a bus connecting the various components together. The system may be coupled to a communication medium, such as a modem connected to a phone line, wireless network, or the Internet.

The present invention is preferably implemented using a general purpose digital computer, microprocessor, microcontroller, or digital signal processor programmed in accordance with the teachings of the present specification, as will be apparent to those skilled in the computer art. Appropriate software coding may be readily be prepared by skilled programmers based on the teachings of the present disclosure, as will be apparent to those skilled in the software art.

The present invention preferably includes a computer program product, which includes a storage medium comprising instructions that can be used to direct a computer to perform processes in accordance with the invention. The storage medium preferably includes, but is not limited to, any type of disk including floppy disks, optical data carriers, compact discs (CD), digital video discs (DVD), magneto-optical disks, read only memory (ROM), random access memory (RAM), electically programmable read only memory (EPROM), electrically eraseable programmable read only memory (EEPROM), magnetic or optical cards, or any type of media suitable for storing information.

Stored on any one of the above described storage media, the present invention preferably includes programming for controlling both the hardware of the computer and enabling the computer to interact with a human user. Such programming may include, but is not limited to, software for implementation of device drivers, operating systems, and user applications. Such storage media preferably further includes programming or software instructions to direct the general purpose computer to perform tasks in accordance with the present invention.

The programming of the computer preferably includes software for digitizing and storing images obtained from the image acquisition device (helical computed tomography scanner). Alternatively, it should be understood that the present invention may also be implemented to process digital data derived from images obtained by other means, such as x-rays and magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, optical tomography, and electrical impedance tomography.

The invention may also be implemented by the preparation of application specific integrated circuits (ASIC), field programmable gate arrays (FPGA), or by interconnecting the appropriate component devices, circuits, or modules, as will be apparent to those skilled in the art.

A. NODULE DETECTION

Referring to Figure 1, the nodule detection algorithm involves four major stages. First, lung regions are segmented from the whole lung computed tomography (CT) scan. This is followed by a hypothesis generation stage. In this stage, nodule candidate regions are identified from the whole lung scan and their size is estimated. In the third stage, the nodule candidate sub-images pass through a streaking artifact removal process. The nodule candidates are successively refined in the fourth stage using filters of increasing complexity.

The region of the image space where pulmonary nodules are to be found is first identified. A distinction is made between the lung parenchyma where spherical nodules are located and the region of lung parenchyma adjacent to solid structures where attached nodules are located, since different techniques are used to detect the two nodule forms. Therefore, two lung regions are identified; the first lung region is the lung parenchyma which is not close to any major solid structure, and the second lung region is a narrow region of lung parenchyma that is adjacent to solid structures. In this context, major solid structures include the chest wall, the hilum region, large

blood vessels and the primary bronchi. An axial slice image and its corresponding segmented regions are shown in Figures 2 through 4.

Pulmonary solid nodules are approximately spherical shaped lesions with a density slightly greater than water. These lesions are identified on routine chest radiographs and/or low resolution CT scans of asymptomatic patients. Pulmonary nodules can be broadly classified into two groups. The first group include nodules with no attachment to a large solid structure These nodules have, in general, a spherical shape. However, the spherical shape may be distorted by other small lung structures such as vessels, bronchi, scars and regions of morbidity. Typically, growing nodules appear to wrap around such structures. An example of such a nodule is shown in Figure 5.

The second group consists of nodules attached to large dense structures, an example of which is shown in Figure 6. In this context, large dense structures refer to those structures with a size comparable to or larger than the nodules diameter. Nodules attached to the pleural surface are the most prevalent of this type. However, nodules may also be attached to other structures such as large vessels, airways and/or the hilum region. In general, the shape of this type of nodule is significantly affected by a large adjacent structure; a nodule that is attached to a pleural surface often has the appearance of a hemisphere with the curved region growing into the lung parenchyma. The images in Figures 5 and 6 were created using light shaded rendering of the surface of the nodule extracted from a high resolution CT image series.

The current radiological size characterization of a nodule is its "diameter" N_R. For CT image scans, this diameter is estimated from a single axial slice from the central region of the nodule. One common method of size estimation is computing the average of the horizontal and vertical extents of the nodule.

For three-dimensional computer image analysis, two parameters are defined: the maximum inscribed sphere (MIS) and the minimum circumscribed sphere (MCS)

that characterize the size and irregularity of a nodule in three-dimensional space. The MIS and MCS are defined with respect to the geometric center of mass (GCOM). The GCOM $N_c = (X_c, Y_c, Z_c)$ is the location of the center of mass of the nodule region assuming a uniform density (I). The GCOM for a nodule is defined as follows:

Let the three dimensional region of the nodule be defined by $f_N(x,y,z)$.

$$f_N(x,y,z) = \begin{cases} 1 : & \text{if } (x,y,z) \text{ lies within the nodule region} \\ 0 : & \text{otherwise} \end{cases}$$

Then, the coordinates of the GCOM $N_c=(X_c, Y_c, Z_c)$ are given by:

$$X_c = \frac{\iiint x \, f_N(x,y,z)\, dx\, dy\, dz}{\iiint f_N(x,y,z)\, dx\, dy\, dz} \qquad (1)$$

$$Y_c = \frac{\iiint y \, f_N(x,y,z)\, dx\, dy\, dz}{\iiint f_N(x,y,z)\, dx\, dy\, dz} \qquad (2)$$

$$Z_c = \frac{\iiint z \, f_N(x,y,z)\, dx\, dy\, dz}{\iiint f_N(x,y,z)\, dx\, dy\, dz} \qquad (3)$$

This measurement does not consider density variations within the nodule but depends only on its geometric form. For a nodule, the minimum distance (R_{MI}) from the nodule geometric center (N_c) to the boundary of the nodule (N_b), specifies the radius of the MIS. That is, the maximum sized sphere that can be inscribed within the nodule centered on N_c.

$$R_{MI} = \min_{\forall i}(D(N_c, N_b^i(x,y,z)))$$

where N_b^i denote the i'th boundary point of the nodule. D denotes the Euclidean distance given by

$$D_E([X_1,Y_1,X_1],[X_2,Y_2,Z_2]) = \sqrt{(X_1 - X_2)^2 + (Y_1 + Y_2)^2 + (Z_1 - Z_2)^2} \quad (4)$$

Similarly the maximum distance (R_{MC}) from N_c to the boundary of the nodule *(Nb)* specifies the radius of the MCS; i.e. the minimum sized sphere that can circumscribe the nodule centered on N_c touching the boundary of the nodule.

$$R_{MC} = \underset{\forall i}{max}(D(N_c, N_b^i(x,y,z)))$$

For the case when a nodule has a highly irregular shape such that N_c does not lie within the nodule, the definition of R_{MI} is further refined to be the minimum distance to the boundary from N_c in which a change from inside to outside the nodule occurs. Similarly, the definition of R_{MC} can be modified to the maximum distance to the boundary from N_c in which a change from inside to outside the nodule occurs. However, such a situation will occur very rarely in practice.

The concepts of R_{MI} and R_{MC} are illustrated on a 2-dimensional example shown in Figure 7. In the Figure, R_{MI} and R_{MC} are the maximum inscribed and minimum circumscribed circle radii for the image region shown respectively. The extension to 3-dimension is straightforward.

In the hypothesis generation stage, nodule candidates are identified from the whole lung scan and their size is estimated. It is critical that no nodules are missed at this stage. However, since the search space is very large, it is also important that this process be computationally efficient. The nodule candidates are refined in the subsequent stages.

First, the lung parenchyma intensity is thresholded using a global threshold parameter (T_g). This parameter can be determined empirically from a training dataset to separate lung parenchyma tissue and high density solid structures. T_g is

preferably determined as approximately the mid-value between the mean value for solid tissue and the mean value for lung parenchyma. A preferred value for T_g is -574 HU. During the thresholding procedure, high density anatomical structure voxels having values higher than T_g are labeled as foreground voxels, creating a binary image.

Let $S(r,c)$ denote a spherical region with radius r centered at point c = $(X_c, Y_c, Z_c,)$. Consider a nodule N and its characteristic spheres ($S(R_{MI}, N_c,)$ and $S(R_{MC}, N_c)$) as illustrated in Figure 7. In general, for a nodule N, the center is always at N_c which may be dropped such that $S(R_{MI})=S(R_{MI}, N_c)$. A binary image representation of this nodule should have the following properties.

a. All voxels within $S(R_{MI})$ should be one.

b. All voxels outside $S(R_{MC})$ should be zero.

c. Within the spherical shell region ($S(R_{MC})$ - $S(R_{MI})$), there will be voxels of both values due to the irregular surface of the nodule.

In order to generate a hypothesis for a nodule of size R_{MI} at a location $P = (x, y, z)$ in the binary lung parenchyma image, the following two criteria be met:

a. "Solid center": A large fraction (T_v) of voxels in $S(R_{MI})$ centered at P must be one.

b. "Limited extent": A large fraction (T_{av}) of voxels in the region ($S(R_{MC} + \delta)$ - $S(R_{MC})$) centered at P must be zero.

where δ is a certain constant distance. The "Solid center" criterion(a) ensures that the nodule consists of a dense mass; the threshold T_v allows for some voxels to be zero due to image noise.

While the nodule is bounded by radius R_{MI}, there may be other dense structures in the lung region some of which may be adjacent or touching the nodule N. The "Limited extent" criterion (b) verifies the finite extent of the nodule region.

However, it also allows a small amount of foreground voxels in the region immediately surrounding the nodule due to adjacent or attached structures. The preferred ranges and values for T_v, T_{av} and δ as noted below were determined empirically from an analysis of a set of images in the training dataset.

The hypothesis generation stage is implemented as follows:

1. For each foreground voxel F_P, compute the maximum inscribed sphere radius, R_{MI}, for which the solid center criterion (a) is true.
2. Select only the voxels with local maximum R_{MI} values.
3. For all voxels identified in step 2, determine the limited extent criterion (b).
4. Make a list of nodule candidates of all voxels which satisfy the limited extent criterion (b) in step 3, including their center coordinates (N_c) and their size estimate R_{MI}.

First, approximate spherical regions are identified and their size is estimated. Kanazawa et al. used gray weighted distance transforms for this purpose. K.Kanazawa, M.Kubo, N.Niki, H.Satoh, H.Ohmatsu, K.Eguchi, N.Moriyama, "Computer Assisted Diagnosis of Lung Cancer Using Helical X-ray CT", Proceedings of ICPR, pp 381-385, 1996. After computing the distance transform, Kanazawa et al. used a thinning procedure to determine the center point of the nodule candidate. In the present invention, a different noise tolerant procedure has been implemented. This procedure makes use of a volume occupancy calculation. Volume occupancy, at a particular foreground voxel (F_p), is defined as the ratio of the number of foreground voxels within a sphere ($S(r, F_p)$) to the volume of the sphere. The procedure is illustrated for a 2D region in Figure 8 where F_p represents any seed pixel in the region R. For a 2D region, a circle is used rather than a sphere and an area coverage is calculated instead of a volume occupancy. The basic idea is to search for a center point pixel location in the region R at which the largest size circle can fit. This pixel corresponds to N_c for region R in Figure 8.

The algorithm starts with an initial point F_p within the region and a circle of certain initial small radius. If the area coverage for this particular circle centered at F_p is greater than the threshold T_v the circle radius is incremented. This is sequentially done until the area coverage is less than T_v. T_v is preferably selected to be in a range between about .70 and 1.00, and most preferably about .80. The final circle size approximates the maximum circle size that can be fit in the region centered at location F_p. This procedure is performed for all the points in the region. Every point in the region would have a maximum circle radius associated with it. The region pixel that registered the largest circle size is marked as the center point and the size is recorded as an estimate of the maximum inscribed circle ($\hat{R}_{MI}$). The computational efficiency of this procedure is significantly improved by updating the region pixels list at every iteration. The extension of this concept to 3D regions is straightforward using a spherical kernel and volume occupancy calculation as described above.

After identifying the center point(N_c) of the nodule candidate region and measuring its maximum inscribed sphere's radius (R_{MI}), the next step is the determination and analysis of the immediately adjacent regions.

The volume occupancy of a spherical shell enclosing the nodule candidate is used to evaluate the degree of attached structures. The inner radius of this shell is $\hat{R}_{MI}$ i.e the estimated maximum inscribed sphere corresponding to R_{MI}. The middle sphere has a radius of $\hat{R}_{MC}$ which is obtained from a precomputed table of values for a given R_{MI}. The outer spherical shell has a preset thickness of δ as shown in Figure 9. The $\hat{R}_{MC}$ can also be calculated as the radius of a sphere having a volume between 2.5 and 3.5 times that of the maximum inscribed sphere, R_{MI}. The preferred value of $\hat{R}_{MC}$ can be calculated as $\sqrt[3]{3} * R_{MI}$. The δ can be calculated as the radius of a sphere with a volume between 5.5 and 6.5 times the maximum inscribed sphere, R_{MI}, minus $\hat{R}_{MC}$. The preferred value of δ can be calculated as $\sqrt[3]{6} * R_{MI} - \hat{R}_{MC}$.

High density voxels in Region C correspond to attached structures. The center location N_c is then labeled as a nodule candidate if the ratio of the total volume (V_c) of high density voxels in the adjacent region C to the nodule candidate volume (V_N) is less than a certain threshold (T_{av}). This rule is referred to as the adjacent region rule (AJR):

$$\frac{V_C}{V_N} \leq T_{av} \qquad (5)$$

where T_{av} is the threshold value. T_{av} is preferably selected to be in a range between about 0.00 and 0.50, and most preferably about .28.

After the initial list of nodule candidates is generated, a subimage for each candidate is preferably generated by clipping a region surrounding each nodule candidate to simplify data management. The subimages are basically segmented from the original whole lung CT scan. In an alternative embodiment of the invention, the subimage generation step could be skipped and the refinements described below (e.g. streaking artifact removal and multi-stage filtering) could be applied to the whole lung CT scan.

The occurrence of CT image artifacts such as streaking poses a major problem for the detection of very small nodules. Streaking artifacts are caused by starvation of the x-ray photon flux and beam hardening effects. A majority of the streaking artifact occur near the patient shoulder area or when the patient arms are inside the scan FOV. Photon deficiency is limited to the projections that pass through both shoulders of the patient and result in a horizontal streaking pattern. Jiang Hsieh, "Generalized adaptive median filters and their application in computed tomography", SPIE, vol. 2298, pp. 662-669, 1994.

Geometric characteristics of nodule candidates are used in the nodule candidate refinement stage. Artifacts deform geometrical properties of nodules

resulting in true nodule elimination. A streaking artifact filter is preferably selectively applied to avoid deformation or elimination of small nodules.

The present invention implements an adaptive streaking artifact removal filtering technique. After nodule candidate generation, individual nodule candidate sub-images are selectively filtered based on the amount of streaking artifact present. For this purpose, streaking artifact quantification metric (S_m) is introduced. This metric is calculated by averaging the square difference between two consecutive rows over the nodule candidate subimage.

$$S_m = \frac{1}{nmp}\sum_{i}^{n}\sum_{j}^{m}\sum_{k}^{p}(\,(I(i,j,k) - I(i,j+1,k))^2 \qquad (6)$$

The metric Sm is defined with respect to a global coordinate system as follows:

the X axis runs between a patient's shoulders;

the Y axis runs between a patient's chest and back; and

the Z axis runs along the length of a patient's body,

where i, j, and k are indices for X, Y and Z coordinates respectively and n,m and p are the dimensions of the subimage in X,Y and Z directions respectively.

A streaking artifact filter is applied for nodule candidate sub-images with a metric value greater than an empirically selected threshold, T_{sar}. The preferred range for T_{sar} is between 55,000 and 65,000 HU^2. The preferred value of T_{sar} is about 60,000 HU^2, which corresponds to a pixel pair variation of about 245 HU. In the present invention, a median filter is implemented. Because of horizontal nature of the streaking artifact, vertical median filters are used. Preferably a vertical median filter of size 1x3 is selected. Figures 10 and 11 illustrate a nodule sub-image before and after streaking artifact removal.

A multi-stage filtering procedure, illustrated in Figure 12, is used to reduce the number of false positive candidate regions. This approach is effective in minimizing

the computation time without sacrificing performance. The present invention preferably employs at least two filters. The first filter removes vessels and large vessel bifurcation points from the nodule candidate list. A large percentage of false positives are eliminated by the first filter. The nodule candidates list is then further refined by the second filter, which removes small bifurcation points. A detailed description of each filter is presented below.

Nodule candidates generated in the hypothesis generation stage include nodules, blood vessels and bifurcation points which passed the AJR criterion. The objective of the first filtering stage is to remove blood vessels and large vessel bifurcation points from the nodule candidate list.

In this first filtering stage, the nodule candidate list is refined based on each nodule candidate's attachment surface area to other structures as shown in Figure 13. For this purpose, a fraction (F_a) of the nodule surface that is attached to other solid structure is calculated by

$$F_a = S_a/S_n \tag{7}$$

where S_n denotes the surface area of the nodule candidate and S_a denotes the attachment surface area to all other structures.

Nodule candidates can be categorized into two groups based on the value of F_a. The first group consists of vessels and large bifurcation points which have high values of F_a. The second group consists of nodules and very small bifurcation points. These nodule candidates have values of F_a smaller than the first group. A threshold can be used to eliminate the first group i.e vessels and large bifurcation points, based on the value of F_a.

To estimate F_a, we need to find the outer surface of the nodule. This is achieved by a region growing algorithm starting from $\hat{R}_{MI}$ and incrementing by a

spherical layer until the anticipated $\hat{R}_{MC}$ is reached. At this point, F_a is computed. $\hat{R}_{MC}$ is obtained from a precomputed table of values for a given R_{MI}.

The current implementation of the procedure is described for a 2D region as follows.

1. $\hat{R}_{MC}$ is obtained from a precomputed table of values for a given R_{MI}.

2. For simplicity and efficiency, a rectangular rather than spherical region growing procedure is used. This is illustrated for a 2D region in Figure 14. Starting with a square region, the size is incremented by one pixel on all sides during every iteration. This iteration is repeated until the size of the square matches $\hat{R}_{MC}$. The pixels at the edges of the square region that are connected to the labeled nodule region are used to estimate $\hat{S}_a$. The labeled nodule region is used to estimate $\hat{S}_n$. The extension to three dimension is straightforward except for the anisotropic sampling space in low resolution CT scans. The 3D region growing algorithm increments at a different rate in the axial direction than in the in-plane direction. This growth rate is inversely proportional to the image resolution. For example, if the ratio of axial to in-plane resolution in an image is 3:1, then three iterations of region growing is performed in the in-plane direction before growing once in the axial direction.

3. $\hat{F}_a$ is estimated from $\hat{S}_a/\hat{S}_n$.

4. If $\hat{F}_a \geq T_a$, the nodule candidate is discarded. T_a is an empirically selected threshold representing the ratio of vessel attachment area to the total surface area of the nodule. T_a is preferably selected to be in a range between about .10 and .45, and most preferably about .24.

After the first filter, the majority of false positives are small (2mm size) vessel bifurcation points. Small vessel bifurcation points occur at junctions of small vessels. During global intensity thresholding procedure in the hypothesis generation stage, small vessels are often eliminated leaving the bifurcation point as a compact shape

region with very small attachment (as shown in Figure 15). This is due to the partial voxels effect. The nodule attachment analysis technique used in the previous stage generally does not identify these situations since the vessels were not present.

The second filter eliminates bifurcation points from the nodule candidate list. A hollow cube with a certain wall thickness is used as shown in Figure 17. The cube has an inner side length determined from nodule candidate radius $\hat{R}_{MI}$ multiplied by a scale factor K and thickness δ_2 empirically selected. The preferred range of K is between 1.5 and 2.5 and is preferably about 2. The thickness δ_2 preferably has a minimum value of 1 and should be large enough to achieve noise insensitivity. The preferred range of δ_2 is between 2 and 6 voxels and is preferably 4 voxels. The volume ratio, A_{vr} is then defined using the volume of the intersection V_{ni} of the cube wall with the nodule candidate region and the nodule candidate volume V_n as shown in equation 8. $\hat{R}_{MI}$ is used to calculate V_n. Bifurcation points have a higher A_{vr} value compared to small nodules. The threshold parameter used for this measure is T_{vv}. The preferred range for T_{vv} is from about -774 to -674 HU, and is most preferably selected to be about -724 HU.

$$A_{vr} = V_{ni}/V_n \tag{8}$$

B. <u>PULMONARY NODULE REGISTRATION</u>

Two high-resolution CT images are needed in order to measure the volume change of a nodule. The nodule is segmented from both CT images, and the percent volume change and the doubling time are calculated. With current methods, the segmentation of the nodule in the first image is independent from the segmentation of the nodule in the second image. The consistency of the nodule segmentation between the two images is improved by comparing the segmentation from the first image with the segmentation from the second image.

A region-of-interest (ROI) is selected for the nodule in both of the CT images. The adaptive threshold is selected for each ROI using the histogram of the region, and both ROIs are then resampled to isotropic space.

To facilitate a meaningful comparison, the second ROI is registered to the first ROI. A rigid-body transformation model is assumed, meaning that in general the structures in the ROIs are confined to only translation and rotation. This is a valid assumption because the registration will be performed on a small focused area in the lungs. Thus, it is not expected that the region will change dramatically with the different levels of inspiration that may occur during the two CT scans. Registering the second nodule to the first nodule will change the location and orientation of the second nodule while preserving its volume and shape.

After rigid-body registration, the nodule from the first image and the nodule from the second image will have the same orientation and position. The nodule is segmented from first image and from the registered second image using gray-level thresholding. The attached vessels are removed using iterative morphological filtering, and any pleural attachments axe removed using an iterative clipping plane.

The nodule segmentation of the two ROIs produces two binary images representing a nodule at two different times. The nodule from the second image has been registered with the nodule in the first image. By looking at the corresponding pixels between the segmented nodules and the threshoddnd images, it is possible to label the pixels in the segmented nodules as nodule repeat pixel, nodule growth pixels, nodule atrophy pixels, or missegmented pixels. The nodule segmentations are adjusted by removing the missegmented pixels. This improves the consistency of the segmentations of the nodule in two different times, thus improving the accuracy of the volume measurements.

The algorithm for the registered segmentation procedure is as follows:

1. Select a Region-Of-Interest for the nodule in the two images.
2. Adaptive thresholding selection.
3. Isotropic resampling.

4. Register the second nodule to the first nodule using the rigid-body transformation.

5. Perform segmentation on both of the nodules:

(a) Gray-level thresholding using adaptive threshold.

(b) Vessel Segmentation using iterative morphological filtering.

(c) Pleural Wall Segmentation using a clipping plane.

6. Rule-Based adjustment of the two nodule segmentations.

The details of each step are explained below.

A typical 3D high-resolution CT scan may contain anywhere from 5 to 30 image slices. Each image slice has a resolution of 512 x 512 pixels. A small cubic region-of-interest with a size of about three times the diameter of the nodule is selected. Selecting a small ROI will reduce the amount of computation needed to register and segment the nodule.

The segmentation of nodule tissue from lung parenchyma can be achieved by either a fixed gray-level threshold or by an adaptive threshold. The threshold is selected by choosing a value that best separates the nodule (foreground) from the lung parenchyma (background), which in the normal case is bimodal intensity histogram (see Figure 18). This separation may be achieved by selection of a threshold that falls at the midpoint between the peaks of each mode of the histogram.

The fixed threshold is selected using the mean values of lung parenchyma and solid nodule tissue compiled over several cases. The mean value of lung parenchyma and solid nodule tissue was determined to be -880 HU and -27 HU, respectively. Thus, the fixed threshold was calculated to be -453 HU.

However, a fixed threshold does not take into account the change in lung parenchyma density due to inspiration of the lungs. A study of CT scans by the inventors determined that the density of the parenchyma around the nodule changed on average 9.7 HU ± stddev 7.0 HU (maximum of 21 HU) between repeat scans of the same patient. Furthermore, it was observed that the lung parenchyma density increases towards the back of the lungs when the patient is on his back because of the accumulation of blood due to gravity. In addition, a fixed threshold is not robust to changes in attenuation values due to differences in X-ray dosage and other CT scan parameters.

Preferably an adaptive threshold is used to improve over the limitations of the fixed threshold. The present invention adaptively selects an optimal threshold for each nodule region-of-interest. Given a nodule region-of-interest, a histogram is calculated between -1024 HU and 476 HU using a bin size of 1 HU. The histogram may be noisy because of the small bin size. Accordingly, the histogram is smoothed by filtering with a Gaussian with a standard deviation of 25 HU. The peak values of parenchyma and solid nodule are expected to be relatively close to the mean values calculated over several cases. Thus, the peak parenchyma value calculated by searching over a range of 200 HU from the ideal value of -880 HU. Similarly, the peak solid nodule value is determined by searching over ±200 HU from the ideal value of -27 HU. Finally, the adaptive threshold is calculated as the midpoint between the two peak values. The adaptive threshold selection algorithm is as follows:

1. Given a nodule region-of-interest:
2. Calculate the histogram, $H(x)$, between -1024 HU and 476 HU with a bin size of 1.
3. Filter $H(x)$ with a Gaussian with stddev of 25 HU.
4. Peak Parenchyma: $v_p = max_{-1024<x<-680}\ H(x)$
5. Peak Nodule: $v_n = \max_{-227<x<173}\ H(x)$
6. Adaptive Threshold: $th_a, = (v_p + v_n)/2$

Figure 18 shows an example histogram of a 12mm nodule. The parenchyma peak and solid tissue peak were determined to be -848 HU and -16 HU respectively. The adaptive threshold was then calculated as -432 HU, as opposed to -453 HU for the fixed threshold. The histogram around the solid-tissue peak is seen in Figure 21. Figures 20 and 21 shows the histogram of an ideal 12mm nodule. The histogram of the real nodule has more voxels in the transition region between parenchyma and solid tissue because it contains partial voxels from small vessels and other objects.

For small nodules less than 5mm in size, the solid-tissue distribution in the histogram is usually obscured by partial voxels from small vessels and noise voxels. In this case, the solid-tissue peak value cannot be found through the histogram. The adaptive thresholding algorithm is modified such that the mean solid-tissue value is fixed at the model value of -27 HU. The adaptive threshold is then calculated as the midpoint between the peak parenchyma value and -27 HU. A histogram of a 5mm nodule appears in Figure 22. The mean solid-tissue value cannot be found because there is no prominent peak on the right side of the histogram.

After the adaptive threshold is determined, the ROI is then resampled into 0.25mm isoptropic space using trilinear interpolation.

The second ROI is registered to the first ROI using a rigid-body transformation. The rigid-body transfor-mation is a function of six parameters: (t_x, t_y, t_z, r_x, r_y, r_z), or translation in x, translation in y, translation in z, rotation about the x-axis, rotation about the y-axis, and rotation about he z-axis, respectively. The rigid-body transformation is a mapping of a point v in 3-d space to a point v' in transformed space defined by the following equation:

$$v'=R_xR_yR_zv+\begin{bmatrix} t_x \\ t_y \\ t_z \end{bmatrix} \qquad (1)$$

where R_x, R_y, and R_z are the rotation matrices defined as:

$$R_x = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(r_x) & -\sin(r_x) \\ 0 & \sin(r_x) & \cos(r_x) \end{bmatrix} \quad (2)$$

$$R_y = \begin{bmatrix} \cos(r_y) & 0 & \sin(r_y) \\ 0 & 1 & 0 \\ -\sin(r_y) & 0 & \cos(r_y) \end{bmatrix} \quad (3)$$

$$R_z = \begin{bmatrix} \cos(r_z) & -\sin(r_z) & 0 \\ \sin(r_z) & \cos(r_z) & 0 \\ 0 & 0 & 1 \end{bmatrix}. \quad (4)$$

The second ROI is registered to the first ROI by conducting a search over the 6 transformation parameters: The search is designed to minimize a similarity metric between the transformed second ROI and the first ROI, thus aligning the two ROI's using the transformation parameters. The mean-squared-difference (MSD) is used as the similarity metric and is defined as

$$MSD = \frac{1}{N} \sum\sum\sum_{i,j,k} (ROI_{2t}(i,j,k) - ROI_1(i,j,k))^2 \quad (5)$$

where N is the number of pixels in ROI_1. With the MSD metric, perfectly registered images will produce a metric of zero. The goal of registration is to align the nodule in the first ROI with the nodule in the second ROI. The MSD metric can be modified by weighting it with an appropriately sized gaussian. The gaussian is positioned over the center of the nodule and has a standard deviation equal to the radius of the nodule. The gaussian-weighted MSD is defined as:

$$MSD = \frac{1}{N} \sum\sum\sum_{i,j,k} exp\left(\frac{\left((g_x - i)^2 + (g_y - j)^2 + (g_z - k)^2\right)}{2g_r^2}\right)(ROI_{2t}(i,j,k) - ROI(i,j,k))^2 \quad (6)$$

where (g_x,g_y,g_z) is the center of the gaussian and g_r is the standard deviation of the gaussian. Using the gaussian-weighted MSD will force the registration algorithm to focus more on aligning the nodule than any periphery structures (e.g. vessels or pleural wall). However, some of the periphery structures are needed for a good registration, thus the size of the gaussian is selected to include all of the nodule and some of its periphery.

The similarity metric is minimized using Powell's method, a multi-dimensional direction-set search algorithm. W. Press, editor. *Numerical Recipes in C*. Cambridge University Press, second edition, 1992. The initial translation parameter is set to the offset of the center of the first nodule to the center of the second nodule. The initial rotation parameters are set to (0,0,0). The search is terminated when either all the transformation parameters change within some epsilon, or the similarity metric does not change by more than a tolerance value. After the registration is complete, the second ROI will be the same size as the first ROI.

An example of rigid-body registration on two nodules is shown in Figure 26. The first ROI and the second ROI are shown in Figures 24 and 25, respectively. The registration algorithm aligned the second ROI with the first ROI using translation parameters of (-13.40,16.61, -0.88) pixels and rotation parameters of (0.79, -3.52,-7.20) degrees. The resulting registered image is seen in Figure 26. Figure 27 shows the difference image between the first ROI and the second ROI. The difference image shows that the vessels at the top of the image and on the right of the image are not aligned properly. The circular white ring is the growth of the nodule between the two scan times. Figure 28 shows the difference image between the first ROI and the registered second ROI. The vessels are less visible in the second difference image than in the first difference image, meaning that with the registered image the vessels and nodule are aligned better than without registration.

A binary image of the solid nodule is created by thresholding the image with the adaptive threshold determined previously. Any attached vessels are removed by

using iterative morphological filtering. A morphological opening, followed by masking with the original binary image, is performed using a decreasing sphere size. The initial diameter of the sphere is 3/4 of the nodule radius, resulting in the removal of all vessels that are smaller than 3/4 of the radius.

If the nodule is juxtapleural, then the pleural surface is segmented from the nodule using a clipping plane approach. Starting at a point inside the nodule, a clipping plane is moved towards the pleural wall. When the relative change in the size of the nodule is over a threshold, the plane is reorientated to minimize the size of the nodule. Finally, the algorithm stops when the reorientation procedure does not produce any significant change in the size of the nodule. The juxtapleural nodule is then segmented by using the clipping plane from the previous iteration.

Figure 29 shows an example of the solid nodule segmentation. A montage of the original gray-scale nodule is shown on in Figure 29, while the segmented nodule is shown in Figure 30. The segmented nodule is shaded in red. The pleural surface and vessels are shaded in green, while the background is shaded in gray. The solid nodule segmentation has detached the vessel and pleural wall from the nodule.

Given the two segmented nodules, it is possible to adjust the nodule segmentations by comparing the segmented nodules and the thresholded regions. Let S_1 be the segmented nodule from the first image and T_1 be the thresholded first image before vessel or pleural surface removal. Likewise, let S_2 be the segmented nodule from the second image and T_2 be the thresholded second image.

A rule-based system is used to mark active pixels in the segmented nodule S_1 as repeat nodule, nodule atrophy, or nodule missegmentation. If an active pixel in the first segmented nodule corresponds to an active pixel in the second segmented nodule, then that pixel is a repeat nodule pixel because it is present in both segmented nodules. If an active pixel in the first segmented nodule corresponds to an inactive pixel in the second segmented nodule and an inactive pixel in the second thresholded image, then that pixel is a nodule atrophy pixel because it is present in the first nodule, but not present in the second image. Finally, if an active pixel in

the first segmented nodule corresponds to an inactive pixel in the second segmented nodule and an active pixel in the second thresholded region, then that pixel is a missegmented nodule pixel because it is a non-nodule object (vessel or pleural wall) in the second region.

An active pixel in the segmented nodule S_2 can be marked as repeat nodule pixel, nodule growth pixel, or nodule missegmented pixel by using a similar set of rules. A summary of the rules for marking a region in S_1 or S_2 are given below.

For a foreground pixel in the first segmented nodule, S_1:

- (A) If the corresponding pixel in S_2 and the corresponding pixel in T_2 are both foreground, then the pixel in S_1 is a repeated nodule pixel from the first region-of-interest (ROI_1) to the transformed second region-of-interest (ROI_{2t}).
- (B) If the corresponding pixel in S_2 is background and the corresponding pixel in T_2 is background, then the pixel in S_1 is nodule atrophy pixel.
- (C) If the corresponding pixel in S_2 is background and the corresponding pixel in T_2 is foreground, then the pixel in S_1 is a missegmented pixel in the first region-of-interest (ROI_1).

For a foreground pixel in the second segmented nodule, S_2:

- (D) If the corresponding pixel in S_1 and the corresponding pixel in T_1 are both foreground, then the pixel in S_2 is a repeated nodule pixel from the first region-of-interest (ROI_1) to the transformed second region-of-interest (ROI_{2t}).
- (E) If the corresponding pixel in S_1 is background and the corresponding pixel in T_1 is background,. then the pixel in S_2 is nodule growth pixel.
- (F) If the corresponding pixel in S_1 is background and the corresponding pixel in T_1 is foreground, then the pixel in S_2 is a missegmented pixel in the transformed second region-of-interest (ROI_{2t}).

Figures 31 through 38 illustrate an example of the segmentation adjustment on a registered vascularized nodule. The thresholded nodule at two different times is shown in Figures 31 and 32, and the segmented nodules are shown in Figures 33 and

34. In the first segmentation part of the top attached vessel has been missegmented as part of the nodule, and in the second segmentation, part of the bottom attached vessel has been missegmented as part of the second nodule. By using the rules described above, the regions of each segmentation are marked in Figures 35 and 36 as (A) nodule in time 1, (B) nodule atrophy, (C) nodule missegmentation in time 1, (D) nodule in time 2, (E) nodule growth, or (F) nodule missegmentation in time 2. Finally, the segmentations of both nodules are adjusted in Figures 37 and 38 by removing the missegmented regions (C) and (F). The volumes of the nodules in the adjusted segmentations are more accurate than the volumes in the original segmentations because the vessel attachments have been removed. This leads to a more accurate determination of doubling time or percent volume change. Furthermore, regions of growth and atrophy of the nodule can be examined over time.

Thus, while there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and is intended to claim all such changes and modifications as fall within the true scope of the invention.